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THE CLINICAL CENTER
DIVISION OF RESEARCH GRANTS

February 20, 1957

Dr. Joshua Lederberg
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The University of Wisconsin
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Dear Josh:

Thanks much for your interesting letter of February 14,
and the comments and suggestions of you and Zinder.

Let me tell you what we have been doing along these
lines:

1. We have been interested in the role of intact bone marrow cells in protection against LD₉₀₋₁₀₀ X-radiation and the relationship of protection to H-2 loci. Antologous bone marrow gives good protection; homologous bone marrow gives some protection, depending upon the host and donor strains used, but in most cases a "secondary disease" syndrome develops leading to ~~anorexia~~ cachexia and specific lesions of the liver, spleen, intestine etc., the degree and severity depending again upon the strains used. This occurs despite complete repopulation of the bone marrow. In F₁ hosts, F₁ bone marrow protects, but the secondary disease develops if either parental bone marrow is used. If one uses an isogenic resistant strain, for example C57BL(H-2^d) and its counterpart C57BL(H-2^b), again the secondary syndrome develops despite the difference at only one locus. Our problem at the moment is in attempting to characterize fully the "secondary disease" and to determine whether or not it is an immunologic phenomenon. Our present thinking is that the donor cells produce antibodies which lead to secondary disease.

2. We are also in the process of screening our reticular neoplasms of the mouse (lymphocytic, granulocytic, monocytic and histiocytic leukemias, multiple myeloma, lymphosarcoma, Hodgkins-disease etc.), in their response to extremely high doses of X-rays (1500 r over 8 hours) followed by immediate protection by antologous bone marrow. One out of 4 neoplasms to date has shown a fairly good response. The feasibility of using homologous bone marrow is limited

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of course by the development of "secondary disease", but nonetheless we hope to give this a try once we develop several good models. The group of Harwell has made some progress in this direction (see Barnes, D.W.H. et al. British Med. Journal 4993: 626, September 1956). I suspect that they are dealing with a rare sensitive neoplasm.

3. We have some data along these lines which may interest you. In several inbred strains and also in F_1 hybrids, a few mice protected with homologous bone marrow have survived the "secondary disease" and lived a rather normal life. In many instances leukemias have arisen in these mice and these are of the genetic constitution of the donor blood cells and not of the host, showing the development of leukemic chimaeras or chimeric leukemias. This is additional evidence of the repopulation of the bone marrow by donor cells.

4. We had postulated, as you have, that if the toxic effects of such chemotherapeutic agents as folic antagonists, purine antagonists and glutamine antagonists were similar to the effects of X-radiation, one should be able to do something about it by repopulating the bone marrow. Unfortunately, this doesn't work (or the effect is extremely subtle) since following long courses of A-methopterin and thioguanine, death still occurs despite a repopulated marrow. We have one lead to follow, and that is a significant increase in leukemic mice (L-4946) treated with A-methopterin and given bone marrow (autologous) over A-methopterin-treated leukemics. I would suspect better results using nitrogen mustard and its derivatives, and we must try this.

References relating to bone marrow protection following X-radiation are numerous and no one reference is available to give a comprehensive, up to date picture. There are no published data, as far as I know, concerning bone marrow effects on drug toxicity, however several people have tried, for example, Kaplan at Stanford and Phillips at Sloan-Kettering.

I enjoy hearing of your thoughts and wish we were closer together. I plan to be in Madison, for the first time, for a day either preceding or following the AACR meetings in Chicago, April 12, 13 and 14. I hope you plan to be there at that time.

We are much interested in obtaining a microbiologist (genetic) with fairly broad interests to whom we could offer a good position. Do you have any suggestions? Sheldon, in all probability, will not be with us after this summer.

Thanks again for writing. I hope I have given you some information on what is being done and what we are thinking along these lines.

Hope to see you some of these days.

Cordially,

Lloyd W. Law

